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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
ARCHIE, NINA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
efiling@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,731	AGGER ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,9,11-17 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *12,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-7, 9, 11, 13-15, and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed 7-16-10. Claims 2 and 20 have been amended. Claims 18-19 have been cancelled. Claims 26-28 are new. Claims 1-2, 6-7, 9, 11-17, and 20-28 are pending. Claims 12 and 16-17 are withdrawn from consideration. Claims 26-28 are new. Claims 1-2, 6-7, 9, 11, 13-15, and 20-28 are currently under examination.

Objections/Rejections Withdrawn

2. In view of the Applicant's amendments and remarks the following objections/rejections are withdrawn.

a) Objection of claim 2 because of the following informally trehalose was misspelled is withdrawn in light of applicant's amendment.

b) Rejection to claims 18-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection) because of the claim limitation "adjuvant comprises a solution prepared from an evaporated mixture of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanum and a solvent", is withdrawn in light of applicant's cancellation of claims (18-19).

c) Rejection of claims 20-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter rejection) because of the claim limitation "a resuspension of an evaporated mixture of a solvent, a surfactant selected from the group consisting of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanum and a solvent", is withdrawn in light of applicant's amendments thereto (20-23).

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 2, 6-7, 11, 13-15, 20, 24-25, and 28 under 35 U.S.C. 103(a) as being unpatentable by Liu et al (US Patent Application 20020044951 Date April 18, 2002), Dascher et al (International Immunology Vol. 15, No. 8, January 2003 pgs. 915-925), Ravindranath et al (US Patent No. 6,218,166 US Publication Date April 17, 2001), and Lindabald et al (Infection and Immunity Vol. 65 No. 2, 1997 pgs. 623-629) for the reasons set forth in the previous Office Action in the rejection of claims 1, 2, 6-7, 11, 13-15, and 24-25.

Applicants arguments filed in response to the 35 U.S.C. 103(a), July 16, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants argue the cited references, either alone or in combination, fail to support a prima facie case of obviousness. Applicants argue Liu does not disclose an "adjuvant" that comprises an apolar fraction of a total lipid extract of a mycobacterium, or a part of the apolar fraction of a total lipid extract but rather, Liu describes the isolation of "nonpeptide antigens" isolated from a lipid extract of Mycobacterium tuberculosis because Liu is concerned with the antigenic properties of M. tuberculosis lipids. Applicants argue there is no data in Liu that relate to the efficacy of the lipid antigens, either as an antigenic component, or as an adjuvant. Applicants argue the skilled artisan would not look to Liu for any guidance relating to adjuvants and Liu would not provide the skilled artisan with any reasonable expectation that mycobacterial lipids could be used as part of an adjuvant.

B) Applicants argue Liu mentions that M. tuberculosis whole lipid extracts can be separated into different polarity classes, there is nothing in Liu that would suggest to the skilled artisan that one should select a particular polarity class of lipids, e.g., the apolar extract or a fraction thereof, as recited in Applicants' present claims, for use in any type of composition, let

alone an adjuvant, e.g. in combination with DDA. Applicants argue Liu suggests to the skilled artisan that it is preferable to have a combination of lipid antigens with different polarities in the composition, in order to achieve an enhanced, specific immune response against M. tuberculosis. Applicants argue the teachings of Liu cannot provide the skilled artisan with any reasonable expectation that the apolar fraction of total lipid extract from a mycobacterium can be successfully combined with DDA, in order to produce an adjuvant. Applicants argue Lui would not look to Dascher for guidance relating to adjuvants and Dascher would not provide the skilled artisan with any reasonable expectation that lipid extracts can be used as an adjuvant. Applicants state Dascher reports that when DDA alone was used as an adjuvant in combination with whole lipid extracts, there was no significant reduction in bacterial burden versus the formulation of the lipids with QS-21 alone or in combination with other adjuvants which did provide a significant reduction in bacterial burden (see Dascher, p. 919, 2nd Col, and Table l). Applicants argue Dascher provides an explanation for the discouraging results with DDA, and suggests that in contrast to QS-21, DDA fails to incorporate into the liposome carrier. Applicants argue the teachings of Dascher would thus lead the skilled artisan to reasonably expect that DDA cannot function with M. tuberculosis lipids as such and the teachings of Dascher would lead the skilled artisan away from combining lipids with DDA from Applicants' presently claimed compositions. Applicants argue Lindabald also does not cure the deficiencies of the cited references discussed above, in order to establish a prima facie case of obviousness because Lindabald hypothesizes that DDA may be useful as an adjuvant in peptide-based vaccines, and Lindabald is completely silent regarding lipid-based vaccines.

C) Applicants argue Ravindranath would not lead the skilled artisan to select the apolar fraction, or part of the apolar fraction of the total lipid extract and there is nothing in Ravindranath that would reasonably lead the skilled artisan to select, from the extensive list of adjuvants described by Ravindranath, which does not even include DDA as one of the numerous exemplary adjuvants. Applicants state the numerous adjuvants listed in Ravindranath are allegedly for use in whole-cell vaccine, and are selected as being capable of incorporation into or conjugation to, the membrane of the cells on which the vaccines are based. Applicants argue Ravindranath is completely silent about DDA, but it is also silent about combining the numerous adjuvants together. Applicants argue Ravindranath would not suggest to the skilled artisan that

one should, or could, combine the apolar fraction, or part of the apolar fraction, of mycobacterial lipid extract with DDA for use as an adjuvant and the skilled artisan would have no reasonable expectation of successfully making an adjuvant from the apolar fraction, or part of the apolar fraction of mycobacterial lipid extract in combination with DDA.

D) Applicants state International Patent Application Publication WO 02/074330 describes a fraction of lipids produced from a petrol layer (presumably comprising the apolar lipids) that has no activity and also demonstrates the results described WO 02/074330 are consistent with Applicants' own data. Applicants argue WO 02/074330 demonstrate that apolar lipids are in fact ineffective as adjuvants unless combined with DDA (See, e.g., Specification at Table 1) and thus, confirms the skilled artisan would have no reasonable expectation of successfully combining the apolar fraction, or part of the apolar fraction of the total lipid extract of mycobacterium with DDA.

E) Applicants submit Exhibit A, a Declaration under 37 C.F.R. §1.131 by Dr. Dennis Christensen, an expert in vaccine formulation confirms that it was appreciated by those skilled in the art that different classes of adjuvants are commonly used for different classes of vaccines. Applicants argue Dr. Christensen confirms that the state of the art regarding which adjuvants will function well, if at all, in the various types of vaccines was unpredictable. Applicants state according to Dr. Christensen, the state of the art as of the effective filing date of the instant application was such that the skilled artisan would have no reasonable expectation that the apolar lipid fraction of mycobacterium could be used in combination with DDA, since the state of the art, as evidenced by Dascher suggested that DDA and total mycobacterial lipid extract did not provide immunopotentiating activity that was as good as other adjuvants.

F) Applicants state in determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103(a) is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious and there must be a reasonable expectation of success. Applicants argue the unexpected results of synergistic efficacy observed within Applicants' claimed compositions are sufficient to rebut any prima facie showing. Applicants provide data that demonstrate that the specific combination of DDA and the apolar fraction of total mycobacterial lipid extract function together synergistically as an adjuvant, and is significantly more effective when compared to other formulations (see

paragraph [0097]). Applicants describe experiments demonstrating that antigen combined with DDA alone does not provide significant adjuvant properties, as measured by the release of IFN-gamma, in response to stimulation with antigen 5 weeks after immunization (see, Specification, at paragraph [0097] and Figure 5). Applicants argue surprisingly the combination of DDA and mycobacterial lipid extract function synergistically as an adjuvant as shown by the greater than additive effect of DDA/lipid extract on IFN-gamma release to provide beneficial adjuvant properties which could not have been predicted given the teachings of the art discussed above. Applicants argue the greater than additive effect of DDA/mycobacterial lipids is evidence of the non-obviousness of Applicants' presently claimed compositions. Applicants have also discovered that the combination of DDA and mycobacterial lipids beneficially provides for a long-lasting cell mediated immune response (see, e.g., specification, at paragraph [0032]).

G) Applicants argue the vaccine formulations using the combination of DDA with apolar lipids elicited about a four-fold more potent immune response compared to DDA combined with total lipid extract, and a five-fold more potent immune response compared to DDA combined with polar lipids, as measured in IFN-gamma release (see specification at Table 7) which leads to a profound cellular (IFN-gamma) immune response to vaccine antigens as compared to the response to DDA combined with total lipid (see specification, at Table 7). Applicants argue Table 8 shows that on the other hand, that the antibody response to vaccine antigens with DDA/apolar lipid extract as an adjuvant is similar to that observed when DDA/total lipids are used as adjuvant (Table 8). Applicants argue the data demonstrate that the apolar fraction, in combination with DDA causes a re-direction of the immune response toward a cellular response and this re-direction is highly desirable for certain purposes, including tuberculosis vaccination. Applicants argue the discovery was unexpected, particularly in light of the disclosure of Dascher, indicating that DDA does not form proper liposomes when combined with lipid extract (see paragraphs [0122] - [0126] of the specification).

Applicants state the apolar lipid fraction alone, or the polar lipid fraction alone did not elicit a significant immune response, thereby confirming the data discussed above showing that the presence of DDA is necessary to achieve the adjuvant effect, thus the synergistic effect of the combination of the apolar lipid fraction and DDA could not have been predicted. Applicants describe additional experiments that demonstrate that DDA, when combined with mycobacterial

lipids, provides an unexpectedly potent adjuvant effect when compared to different liposomal formulations and the significant increase in efficacy of the specific combination of the apolar lipid fraction and DDA in functioning as an adjuvant could not have been predicted. Applicants argue the specific combination of DDA and mycobacterial lipid extracts elicited a much higher immune response (as measured by IFN-3, release), compared to any of the other formulations tested, including DOTAP, another cationic surfactant (see Figure 9). Applicants argue neither neutral liposomes nor anionic liposomes, when combined with mycobacterial lipid extract elicited an immune response. Applicants argue the advantage of formulating a vaccine with DDA and lipids from the apolar class only could not have been foreseen from any of the cited references, particularly in view of Liu, which suggest the benefits of using a combination of lipids with different polarities.

H) Applicants' surprising results to the unexpected effects of the specific combination of DDA and mycobacterial lipids has been confirmed in further studies, i.e., Rosenkrands et al. (2005) Infect. Immun. 73(9): 5817-5826 ("Rosenkrands," submitted herewith as Exhibit C). Rosenkrands is an article published after the effective filing, date of the instant Application, and co-authored by the inventor of the instant Application. Applicants state the Christensen Declaration confirms the unexpected effectiveness of the presently claimed compositions shown in the later publication by Rosenkrands. Applicants state Rosenkrands examined the immunogenic effect of various vaccines having Ag85B- ESAT6 as the immunogenic component, and different adjuvants with DDA, to DOTA, DC-Chol, DOPE, or hydrogel. Applicants argue the results of the experiments are shown in Figure 2 of Rosenkrands and the level of IFN-gamma, release in mice immunized with antigen and an adjuvant comprising DDA and total mycobacterial (BCG) lipids, which comprises the apolar fraction, are far superior at stimulating IFN-3, release, compared to any of the other co- adjuvants tested. Applicants state the DDA and mycobacterial lipids adjuvant also resulted in a considerable antibody response to Ag85B-ESAT6, when compared to DOTA, DC-Chol, DOPE, or hydrogel.

Applicants argue Rosenkrands provides data confirming Applicants' discovery that the claimed compositions provide improved long-term resistance compared to other vaccines. Rosenkrands shows that beyond six months after immunization, DDA/mycobacterial lipids/Ag85B-ESAT6 provides significantly higher resistance to M. tuberculosis infection, as

compared to the M. tuberculosis BCG vaccine (see, Rosenkrands, Fig. 6). Rosenkrands discusses the possible mechanisms responsible for the effects of DDA on duration of protection evidenced by earlier studies Katz et al. 1996 (ref. 22) showing antibody responses of lower duration and more recent studies by Holten-Andersen et al. 2004 (ref. 19) proposing that DDA forms a depot ensuring slow release of antigen. However, Rosenkrands emphasizes that studies with DDA alone never resulted in such striking levels of long-term memory immune responses as seen with the cationic liposomes incorporating apolar mycobacterial lipids, and that the mycobacterial lipids must play an important role: possibly, resistance of the lipids (e.g. phthiocerol dimycoserosates which are part of the apolar fraction) to degradation contribute to the long-term effect (page 5825, 2na paragraph). Applicants argue the interplay between mycobacterial lipids and DDA could not have been predicted in view of the teachings of the cited art.

I) Applicants state Dr. Christensen explains that the data on table 3 on page 5824 in Rosenkrands presents results showing vaccine protection against infection with M. tuberculosis resulting in an increased duration of the immune response resulting from DDA based liposomes with mycobacterial lipids (mycosomes), as compared to DDA alone, or DDA combined with MPL (a known immunomodulator), thus Dr. Christensen shows that DDA alone is ineffective as adjuvant, and that the effect of using mycobacterial lipids alone is no more than modest (see Rosenkrands Table 2; Christensen Declaration). Applicants state Rosenkrands show "a markedly stronger immune response induced when mycobacterial lipids were administered in combination with cationic liposomes compared to other liposomes, the cationic DDA stood out as the most efficient vehicle in terms of both antibody production and IFN-gamma levels induced" (see page 5824, 2nd column, last paragraph). Applicants argue the effect of combining mycobacterial lipids and DDA in cationic liposomes exhibited more than an additive effect when compared to either component alone, demonstrating that the DDA and mycobacterial lipid extract functions synergistically (see Rosenkrands, Table 1; Christensen Declaration).

Examiners Response to Applicants Arguments:

With regard to Point (A), Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach

the fractionation of nonpeptide antigens with solvents such as methanol and chloroform (see [0031]). The specification define apolar lipid fraction is defined as non-polar lipids and the apolar lipid fraction is obtained by treating mycobacterium with a biphasic mixture of methanol/saline and petroleum ether whereby the lipid fraction is obtained by addition of chloroform. Hence said apolar fraction or part of total lipid extract of a mycobacterium are deemed to be the same as the apolar fraction or part of total lipid extract of a mycobacterium recited in the instant claims. Therefore Lui et al meet the limitation of apolar fraction or part of total lipid extract of a mycobacterium. Moreover, the efficacy of the lipid antigens either as an antigenic component, or as an adjuvant are inherent characteristics of said apolar fraction or part of total lipid extract of a mycobacterium and hence the apolar fraction or part of total lipid extract of Lui would have all the immunological characteristics of the instant invention. Therefore Lui et al meet the limitations. Applicants response that one the skilled artisan would not have any reasonable expectation that mycobacterial lipids could be used as part of an adjuvant is unpersuasive the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to Point (B), In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with solvents such as methanol and chloroform (see [0031]). The specification define apolar lipid fraction is defined as non-polar lipids and the apolar lipid fraction is obtained by treating mycobacterium with a biphasic mixture of

methanol/saline and petroleum ether whereby the lipid fraction is obtained by addition of chloroform. Hence said apolar fraction or part of total lipid extract of a mycobacterium are deemed to be the same as the apolar fraction or part of total lipid extract of a mycobacterium recited in the instant claims. Therefore Lui et al meet the limitation of apolar fraction or part of total lipid extract of a mycobacterium. Moreover, Dascher et al teach immunization with a mycobacterial lipid vaccine comprising *Mycobacterium tuberculosis* lipids and DDA (see abstract and pg. 917 column 1 last paragraph). Dascher et al teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 916 column 2 last paragraph) and used cholesterol as carrier lipids.

One would be motivated to modify the composition comprising fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium (as disclosed by Lui et al) by incorporating DDA (as disclosed by Dascher et al) into a composition in order to take advantage of effective vaccine against Mycobacterium tuberculosis (as disclosed by Lindabald). One would have a reasonable expectation of success because to using an adjuvant and an apolar fraction or part of total lipid extract of a mycobacterium (as disclosed Lui et al) is well known in the art.

Furthermore Lui et al. teach useful adjuvants comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium that can be used in vaccines is known in the art. Dascher et al teach a mycobacterial lipid vaccine comprising the combination of *Mycobacterium tuberculosis* lipids and DDA as being well known in the art.

Given that Lui demonstrates apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant and the adjuvant can be used in a vaccine are well established in the art and Dascher et al teach a mycobacterial lipid vaccine comprising the combination of *Mycobacterium tuberculosis* lipids and DDA as being well known in the art. The apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant of Lui et al is well within the capabilities of one of ordinary skill in the art to be obvious to try any and all combinations of known adjuvants with a given antigen. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using

the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

Moreover, the relevance of the reference Lindabald is to provide motivation to combine the teachings of Lui et al and Dascher et al, whereby it would be obvious to incorporate the DDA (disclosed by Dascher et al) into the adjuvant (disclosed by Lui et al) because the immune responses induced by the adjuvant DDA increases the efficiency of a TB (Tuberculosis) subunit vaccine (see Lindabald et al see abstract) aforementioned above. Moreover, in all, contrary to Applicant's assertion, there is nothing in the teachings of Dascher et al that would lead the skilled artisan away from combining lipids with DDA from Applicants' presently claimed compositions.

With regard to Point (C), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The relevance of Ravindranath et al. is teaching adjuvants may be provided as purified components, in a partially purified state, or even as a membrane preparation or cellular extract, so long as the active components of such compositions can be incorporated into the cell itself or associated with, integrated into, or conjugated to the membrane of the target cell such as phenolic glycolipids (see Table 1). Moreover when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the *Merck Index*, saying that "the tenth edition of the *Merck Index* lists ten thousand compounds. In our view, each and every one of those compounds is 'described' as that term is used in 35 U.S.C. § 102(a), in that publication."). *Id.* at 1718. (See MPEP 2131.02). Therefore Applicants response of an extensive list of adjuvants described by Ravindranath which does not even include DDA as one of the numerous exemplary adjuvants is unpersuasive.

Furthermore given that Ravindranath et al. teach useful adjuvants that can be conjugated to cellular vaccines are whole or part of cell phenolic glycolipids (see Table 1). It remains obvious to incorporate phenolic glycolipids or trehalose mycolates (as disclosed Ravindranath et al.) into an adjuvant because adjuvant-incorporated cell compositions are useful in methods to significantly improve immune responses and may be employed to stimulate or increase the antibody or T cell responses against intracellular or membrane-bound antigens, even those that are otherwise poor immunogens. Moreover, Applicants argument that the one skilled artisan would not be lead to combine the apolar fraction, or part of the apolar fraction of the total lipid extract with nothing in Ravindranath is unpersuasive. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

With regard to Point (D) the International Patent Application Publication WO 02/074330 describes a fraction of lipids produced from a petrol layer (presumably comprising the apolar lipids) that failed to drive a Th1 response (see example 2) not any activity. Therefore Applicants arguments that the results described in WO 02/074330 might be consistent with Applicants' own data is unpersuasive and does not confirm that the skilled artisan would have no reasonable expectation of successfully combining the apolar fraction, or part of the apolar fraction of the total lipid extract of mycobacterium with DDA.

With regard to Point (E) the Declaration signed by Dr. Dennis Christensen is not in commensurate in scope with the instant claims because none of the instant claim are limited to the specific antigen/adjuvant that was demonstrated to show a synergistic effect. Additionally, the claims don't require the adjuvant to have any particular activity. Christensen disclose one cannot predict the efficacy of a given adjuvant with a given antigen (i.e efficacy of a given antigen is antigen dependent). Therefore although there are several adjuvants known one cannot predict which adjuvants would be particularly effective with other co-adjuvants, or with various antigenic components. The Declaration by Christensen confirms the fact that there are very few adjuvants that can be used in humans and the fact that one cannot predict which antigen/adjuvant

combinations will have efficacy the motivation that would lead the skilled artisan to try all combinations. The Declaration by Christensen confirms because very few adjuvants can be used in humans and cannont predict one which antigen/adjuvant combinations will have efficacy, one skilled in the art would reduce to practice to try any all combination that would lead the skilled artisan to the claimed invention.

With regard to Points (F) and (G), Applicants stating the unexpected results of synergistic efficacy seen with the claimed invention shown in the examples aforementioned above that would not have been expected from the cited art is unpersuasive the instant claims are not limited to the specific antigen/adjuvant that was demonstrated to show a synergistic effect. Additionally, the claims don't require the adjuvant to have any particular activity. Furthermore, the results of unexpected activity seen with the claimed invention shown in the examples and the data in Tables 7-8 and Figure 9 aforementioned above is unpersuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Therefore it is not necessary that the prior art achieve the same advantage or result discovered by Applicant. The rejection does not include knowledge gleaned only from Applicant's disclosure and the motivation to combine can be different than Applicants. Moreover, it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Applicant. MPEP 2144(IV). In the instant case, Liu et al, Dascher et al, Ravindranath et al, and Lindabald et al, do not need to suggest the combination to achieve the same advantage or result discovered by Applicant. Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel difference between the claimed product and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Additionally Applicant is reminded "the claiming of a new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Consequently, the mere discovery of the combination of DDA and apolar or part of the apolar fraction of a total polar lipid extract of a mycobacterium does not impart novelty to the adjuvant.

Moreover, Applicants assertion that the advantage of formulating a vaccine with DDA and lipids from the apolar class only could not have been foreseen from any of the cited references is unpersuasive for the reasons stated in the in the Declaration by Christensen. The Declaration by Christensen confirms although there are several adjuvants known one cannot predict which adjuvants would be particularly effective with other co-adjuvants, or with various antigenic components. The Declaration by Christensen confirms the fact that there are very few adjuvants that can be used in humans and the fact that one cannot predict which antigen/adjuvant combinations will have efficacy providing the motivation that would lead the skilled artisan to try all combinations. The Declaration by Christensen confirms because very few adjuvants can be used in humans and cannont predict one which antigen/adjuvant combinations will have efficacy, one skilled in the art would reduce to practice to try any all combination that would lead the skilled artisan to the claimed invention.

With regard to Points (H) and (I), the reference Rosenkrands discloses a TH1 adjuvant system combining a specific antigen OVA and DDA to determine its synergistic effect (see abstract). Rosenkrands is unpersuasive because the effects of the synergism are only for the combination in the adjuvant system comprising a specific antigen. Furthermore, the results of the experiments shown in Figure 2 and 6 of Rosenkrands and the data on table 3 on page 5824 in Rosenkrands confirming Applicants' discovery and unexpected activity as set forth supra is unpersuasive because the claims are not limited to the specific antigen set forth in Rosenkrands. Consequently, the instant claims are not limited to the specific antigen/adjuvant that was demonstrated to show a synergistic effect set forth in Rosenkrands because the claims are limited to antigenic fragments. Moreover Applicants assertions that Rosenkrands emphasizes that DDA used alone and never resulted in such striking levels of long-term memory immune responses as seen with the cationic liposomes and the data proposing that DDA forms a depot ensuring slow release of antigen is unpersuasive. Moreover, Applicants assertion that DDA does not form proper liposomes when combined with lipid extract is unpersuasive because one skilled in the art would know how to produce the claimed invention in view of the prior art as being obvious.

Moreover, the combination of the prior art of Lui et al, Dascher et al, Ravindranath et al, and Lindabald et al discloses the claimed invention and the mere discovery of the combination of DDA and apolar or part of the apolar fraction of a total polar lipid extract of a mycobacterium

does not impart novelty to the adjuvant. The rejection does not include knowledge gleaned only from Applicant's disclosure and the motivation to combine can be different than Applicants. Moreover, it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Applicant. MPEP 2144(IV). Since the Office does not have the facilities for examining and comparing the product of the instant invention with the product disclosed in the prior art, the burden is on Applicant to show a novel difference between the claimed product and the product of the prior art. See In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Additionally Applicant is reminded "the claiming of a new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

As outlined previously the claims are drawn to an adjuvant comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium (claim 1), wherein the part of the apolar fraction of the lipid extract is selected from the group consisting of phthiocerol dimycocerosates, trehalose mycolipenates, glycosylated phenol phthiocerols, trehalose mycolates, sulfolipids, triacylglycerols and menaquinones (claim 2), a vaccine comprising the adjuvant (claim 6), wherein said vaccine is formulated for parenteral, oral or mucosal administration (claim 7), a delivery system comprising the adjuvant (claim 11), wherein said mycobacterium is *BCG, M. microti, M. tuberculosis or M. vaccae* (claim 13), wherein glycosylated phenol phthiocerols are phenolic glycolipids (claim 14), wherein said mycobacterium is selected from the group consisting of *M. tuberculosis, M. bovis and M. africanum* (claim 15); an adjuvant consisting essentially of a mixture of a solvent, DDA, and an apolar fraction of a total lipid extract of *BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis, or M. africanum* (claim 20), an immunogenic composition comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium, wherein said composition comprises an antigenic component comprising an antigenic epitope (claim 24), an immunogenic composition comprising the adjuvant (claim 25), wherein said part of the apolar fraction of a total lipid extract of a mycobacterium comprises lipids selected from the group

consisting of: phthiocerol dimycocerosates, trehalose mycolipenates, trehalose mycolates, sulfolipids, triacylglycerols and menaquinones (claim 28).

Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with a solvents such as methanol and chloroform (see [0031]). Lui et al teach a vaccine comprising the adjuvant, wherein vaccine is formulated for parenteral, oral or mucosal administration (see paragraphs [0048] and [0054]). Liu et al teach a delivery system comprising an adjuvant (see paragraph [0045]). Liu et al teach composition comprising an antigen isolated from *M. tuberculosis* (see abstract). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims).

Lui et al does not teach an adjuvant comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA), wherein the part of the apolar fraction of the lipid extract is selected from the group consisting of phthiocerol dimycocerosates, trehalose mycolipenates, glycosylated phenol phthiocerols, trehalose mycolates, sulfolipids, triacylglycerols and menaquinones, wherein glycosylated phenol phthiocerols are phenolic glycolipids, an immunogenic composition comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium, wherein said composition comprises an antigenic component comprising an antigenic epitope, an immunogenic composition comprising the adjuvant.

Dascher et al teach immunization with a mycobacterial lipid vaccine comprising *Mycobacterium tuberculosis* lipids and DDA (see abstract and pg. 917 column 1 last paragraph). Dascher et al teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 916 column 2 last paragraph) and used cholesterol as carrier lipids.

Ravindranath et al teach adjuvant-incorporated cell composition and methods for enhancing the antibody and T cell response to cellular antigens by incorporating an immunopotentiating agent into the cellular membrane or into an intracellular compartment to

increase immune responses against. Ravindranath et al teach an adjuvant, wherein part or whole of cell of Mycobacterial species of phenolic glycolipids or trehalose mycolates (i.e. trehalose monomycolate, trehalose dimycolate) (see Table 1) wherein the part of the apolar fraction of the lipid extract is glycosylated phenol phthiocerols, wherein said glycosylated phenol phthiocerols are phenolic glycolipids (see Table 1).

Given that Lui demonstrates apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant and the adjuvant can be used in a vaccine are well established in the art and Dascher et al teach a mycobacterial lipid vaccine comprising the combination of *Mycobacterium tuberculosis* lipids and DDA as being well known in the art. The apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant of Lui et al is well within the capabilities of one of ordinary skill in the art to be obvious to try any and all combinations of known adjuvants with a given antigen. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

Furthermore given that Ravindranath et al. teach useful adjuvants comprising whole or part of cell phenolic glycolipids that can be conjugated to cellular vaccines (see Table 1) and since the use phenolic glycolipids or trehalose mycolates as adjuvants in vaccine compositions is known in the art leading to predictable results, it would be obvious to use cited phenolic glycolipids as taught by Ravindranath et al. into the adjuvant as taught by Liu et al. Thus, it remains obvious to combine them (Ravindranath et al. and Liu et al), even without an express statement of motivation. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

4. Claims 1, 6-7, 9, 11, 13, 15, and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable by Liu et al (US Patent Application 20020044951 Date April 18, 2002), Dascher et al (International Immunology Vol. 15, No. 8, January 2003 pgs. 915-925), Anderson et al (US Patent Application 20020176867 Date November 28, 2002), and Lindabald et al (Infection and Immunity Vol. 65 No. 2, 1997 pgs. 623-629) for the reasons set forth in the previous Office Action in the rejection of claims 1, 6-7, 9, 11, 13, 15, and 20-25.

Applicants arguments filed in response to the 35 U.S.C. 103(a), July 16, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants argue the cited references, either alone or in combination, fail to support a prima facie case of obviousness. Applicants argue Liu does not disclose an "adjuvant" that comprises an apolar fraction of a total lipid extract of a mycobacterium, or a part of the apolar fraction of a total lipid extract but rather, Liu describes the isolation of "nonpeptide antigens" isolated from a lipid extract of Mycobacterium tuberculosis because Liu is concerned with the antigenic properties of M. tuberculosis lipids. Applicants argue there is no data in Liu that relate to the efficacy of the lipid antigens, either as an antigenic component, or as an adjuvant. Applicants argue the skilled artisan would not look to Liu for any guidance relating to adjuvants and Liu would not provide the skilled artisan with any reasonable expectation that mycobacterial lipids could be used as part of an adjuvant.

B) Applicants argue Liu mentions that M. tuberculosis whole lipid extracts can be separated into different polarity classes, there is nothing in Liu that would suggest to the skilled artisan that one should select a particular polarity class of lipids, e.g., the apolar extract or a fraction thereof, as recited in Applicants' present claims, for use in any type of composition, let alone an adjuvant, e.g. in combination with DDA. Applicants argue Liu suggests to the skilled artisan that it is preferable to have a combination of lipid antigens with different polarities in the composition, in order to achieve an enhanced, specific immune response against M. tuberculosis. Applicants argue the teachings of Liu cannot provide the skilled artisan with any reasonable expectation that the apolar fraction of total lipid extract from a mycobacterium can be successfully combined with DDA, in order to produce an adjuvant. Applicants argue Lui would not look to Dascher for guidance relating to adjuvants and Dascher would not provide the skilled

artisan with any reasonable expectation that lipid extracts can be used as an adjuvant. Applicants state Dascher reports that when DDA alone was used as an adjuvant in combination with whole lipid extracts, there was no significant reduction in bacterial burden versus the formulation of the lipids with QS-21 alone or in combination with other adjuvants which did provide a significant reduction in bacterial burden (see Dascher, p. 919, 2nd Col, and Table l). Applicants argue Dascher provides an explanation for the discouraging results with DDA, and suggests that in contrast to QS-21, DDA fails to incorporate into the liposome carrier. Applicants argue the teachings of Dascher would thus lead the skilled artisan to reasonably expect that DDA cannot function with M. tuberculosis lipids as such and the teachings of Dascher would lead the skilled artisan away from combining lipids with DDA from Applicants' presently claimed compositions. Applicants argue Lindabald also does not cure the deficiencies of the cited references discussed above, in order to establish a prima facie case of obviousness because Lindabald hypothesizes that DDA may be useful as an adjuvant in peptide-based vaccines, and Lindabald is completely silent regarding lipid-based vaccines.

C) Applicants argue Ravindranath would not lead the skilled artisan to select the apolar fraction, or part of the apolar fraction of the total lipid extract and there is nothing in Ravindranath that would reasonably lead the skilled artisan to select, from the extensive list of adjuvants described by Ravindranath, which does not even include DDA as one of the numerous exemplary adjuvants. Applicants state the numerous adjuvants listed in Ravindranath are allegedly for use in whole-cell vaccine, and are selected as being capable of incorporation into or conjugation to, the membrane of the cells on which the vaccines are based. Applicants argue Ravindranath is completely silent about DDA, but it is also silent about combining the numerous adjuvants together. Applicants argue Ravindranath would not suggest to the skilled artisan that one should, or could, combine the apolar fraction, or part of the apolar fraction, of mycobacterial lipid extract with DDA for use as an adjuvant and the skilled artisan would have no reasonable expectation of successfully making an adjuvant from the apolar fraction, or part of the apolar fraction of mycobacterial lipid extract in combination with DDA.

D) Applicants argue Anderson is completely silent regarding lipid extracts, and their use in combination with DDA as an adjuvant and provides no guidance that would lead the skilled artisan to believe that one could successfully combine the apolar fraction of a mycobacterial lipid

extract with DDA to achieve an adjuvant, particularly in view of the teachings expressly against such combination.

Examiners Response to Applicants Arguments:

With regard to Point (A), Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with solvents such as methanol and chloroform (see [0031]). The specification define apolar lipid fraction is defined as non-polar lipids and the apolar lipid fraction is obtained by treating mycobacterium with a biphasic mixture of methanol/saline and petroleum ether whereby the lipid fraction is obtained by addition of chloroform. Hence said apolar fraction or part of total lipid extract of a mycobacterium are deemed to be the same as the apolar fraction or part of total lipid extract of a mycobacterium recited in the instant claims. Therefore Lui et al meet the limitation of apolar fraction or part of total lipid extract of a mycobacterium. Moreover, the efficacy of the lipid antigens either as an antigenic component, or as an adjuvant are inherent characteristics of said apolar fraction or part of total lipid extract of a mycobacterium and hence the apolar fraction or part of total lipid extract of Lui would have all the immunological characteristics of the instant invention. Therefore Lui et al meet the limitations. Applicants response that one the skilled artisan would not have any reasonable expectation that mycobacterial lipids could be used as part of an adjuvant is unpersuasive the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With regard to Point (B), In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21

USPQ2d 1941 (Fed. Cir. 1992). Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with solvents such as methanol and chloroform (see [0031]). The specification define apolar lipid fraction is defined as non-polar lipids and the apolar lipid fraction is obtained by treating mycobacterium with a biphasic mixture of methanol/saline and petroleum ether whereby the lipid fraction is obtained by addition of chloroform. Hence said apolar fraction or part of total lipid extract of a mycobacterium are deemed to be the same as the apolar fraction or part of total lipid extract of a mycobacterium recited in the instant claims. Therefore Lui et al meet the limitation of apolar fraction or part of total lipid extract of a mycobacterium. Moreover, Dascher et al teach immunization with a mycobacterial lipid vaccine comprising *Mycobacterium tuberculosis* lipids and DDA (see abstract and pg. 917 column 1 last paragraph). Dascher et al teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 916 column 2 last paragraph) and used cholesterol as carrier lipids.

One would be motivated to modify the composition comprising fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium (as disclosed by Lui et al) by incorporating DDA (as disclosed by Dascher et al) into a composition in order to take advantage of effective vaccine against Mycobacterium tuberculosis (as disclosed by Lindabald). One would have a reasonable expectation of success because to using an adjuvant and an apolar fraction or part of total lipid extract of a mycobacterium (as disclosed Lui et al) is well known in the art.

Furthermore Lui et al. teach useful adjuvants comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium that can be used in vaccines is known in the art. Dascher et al teach a mycobacterial lipid vaccine comprising the combination of *Mycobacterium tuberculosis* lipids and DDA as being well known in the art.

Given that Lui demonstrates apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant and the adjuvant can be used in a vaccine are well established in the art and Dascher et al teach a mycobacterial lipid vaccine comprising the combination of *Mycobacterium tuberculosis* lipids and DDA as being well known in the art. The apolar fraction or part of total lipid extract of a mycobacterium as an effective adjuvant of Lui et al is well within the capabilities of one of ordinary skill in the art to be obvious to try any and all combinations of known adjuvants with a given antigen. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

With regard to Point (C), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The relevance of Ravindranath et al. is teaching adjuvants may be provided as purified components, in a partially purified state, or even as a membrane preparation or cellular extract, so long as the active components of such compositions can be incorporated into the cell itself or associated with, integrated into, or conjugated to the membrane of the target cell such as phenolic glycolipids (see Table 1). Moreover when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the *Merck Index*, saying that "the tenth edition of the *Merck Index* lists ten thousand compounds. In our view, each and every one of those compounds is 'described' as that term is used in 35 U.S.C. § 102(a), in that publication."). *Id.* at 1718. (See MPEP 2131.02). Therefore Applicants response of an extensive

list of adjuvants described by Ravindranath which does not even include DDA as one of the numerous exemplary adjuvants is unpersuasive.

Furthermore given that Ravindranath et al. teach useful adjuvants that can be conjugated to cellular vaccines are whole or part of cell phenolic glycolipids or trehalose mycolates (see Table 1). It remains obvious to incorporate phenolic glycolipids (as disclosed Ravindranath et al.) into an adjuvant because adjuvant-incorporated cell compositions are useful in methods to significantly improve immune responses and may be employed to stimulate or increase the antibody or T cell responses against intracellular or membrane-bound antigens, even those that are otherwise poor immunogens. The KSR decision sets forth "if a technique has been used to improve one device, and a person of skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill". Given that combining adjuvants with various antigens is well within the capabilities of one of ordinary skill in the art, the requirements of obviousness under the KSR decision are met.

Moreover, Applicants argument that the one skilled artisan would not be lead to combine the apolar fraction, or part of the apolar fraction of the total lipid extract with nothing in Ravindranath is unpersuasive.

With regard to Point (D), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with solvents such as methanol and chloroform (see [0031]). The specification define apolar lipid fraction is defined as non-polar lipids and the apolar lipid fraction is obtained by treating mycobacterium with a biphasic mixture of methanol/saline and petroleum ether whereby the lipid fraction is obtained by addition of chloroform. Hence said apolar fraction or part of total lipid extract of a mycobacterium are deemed to be the same as the apolar fraction or part of total lipid extract of a mycobacterium recited in the instant claims.

Therefore Lui et al meet the limitation of apolar fraction or part of total lipid extract of a mycobacterium. The relevance of the teaching of Anderson is disclosing a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis. Anderson et al teach a vaccine, wherein immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis (see abstract, claims, 0027, 0079, whole document in its entirety). Moreover, Dascher et al teach immunization with a mycobacterial lipid vaccine comprising *Mycobacterium tuberculosis* lipids and DDA (see abstract and pg. 917 column 1 last paragraph). Dascher et al teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 916 column 2 last paragraph) and used cholesterol as carrier lipids.

Furthermore given that Anderson et al (2002/0176867) teach a tuberculosis vaccine comprising the immunodominant antigens ESAT-6 and Ag85B from *Mycobacterium tuberculosis*. The skilled artisan would have been motivated to use of said antigens in the compositions of Dascher et al. and Lui et al. in order to take advantage clearing or controlling an infection of the virulent bacteria (as disclosed by Anderson et al.) Moreover, since the use of immunodominant antigens ESAT-6 and Ag85B a vaccine composition is known in the art leading to predictable results, their use remains obvious even without an express statement of motivation. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

Therefore, Applicants assertion that Anderson provides no guidance that would lead the skilled artisan to believe that one could successfully combine the apolar fraction of a mycobacterial lipid extract with DDA to achieve an adjuvant is unpersuasive.

As outlined previously the claims are drawn to an adjuvant comprising are dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium (claim 1), a vaccine comprising the adjuvant (claim 6), wherein said vaccine is formulated for parenteral, oral or mucosal administration (claim 7), wherein the vaccine comprises an antigenic component, and wherein said antigenic component comprises an ESAT6-Ag85B hybrid or a fragment thereof (claim 9), a delivery system comprising the adjuvant (claim 11), wherein said mycobacterium is

M. microti, M. tuberculosis or M. vaccae (claim 13), wherein said mycobacterium is selected from the group consisting of *M. tuberculosis, M. bovis and M. africanum* (claim 15); an adjuvant consisting essentially of a mixture of a solvent, DDA, and an apolar fraction of a total lipid extract of *BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis, or M. africanum* (claim 20), an immunogenic composition comprising an adjuvant and a tuberculosis antigen (claim 21), wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof (claim 22), wherein surfactant is DDA (claim 23); an immunogenic composition comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium, wherein said composition comprises an antigenic component comprising an antigenic epitope (claim 24), an immunogenic composition comprising the adjuvant (claim 25), further comprising a tuberculosis antigen (claim 26), wherein said tuberculosis antigen comprises an ESAT6-Ag85B hybrid or a fragment thereof (claim 27).

Liu et al teach fractionation of nonpeptide antigens isolated from a lipid extract of Mycobacterium tuberculosis wherein the nonpeptide antigens are nonpolar comprising surfactants (see abstract, [0031], [0059]), which correlate to an adjuvant comprising surfactants and an apolar fraction or part of total lipid extract of a mycobacterium. Liu et al teach the fractionation of nonpeptide antigens with a solvents such as methanol and chloroform (see [0031]). Lui et al teach a vaccine comprising the adjuvant, wherein vaccine is formulated for parenteral, oral or mucosal administration (see paragraphs [0048] and [0054]). Liu et al teach a delivery system comprising an adjuvant (see paragraph [0045]). Liu et al teach composition comprising an antigen isolated from *M. tuberculosis* (see abstract). Liu et al teach an adjuvant wherein mycobacterium is *M. tuberculosis* (see claims).

Lui et al does not teach an adjuvant comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA), an immunogenic composition comprising dimehtyldioctadecylammonium-bromide, -chloride, -phosphate, or -acetate (DDA) and an apolar fraction or part of the apolar fraction of a total lipid extract of a mycobacterium, wherein said composition comprises an antigenic component comprising an antigenic epitope, an immunogenic composition comprising the adjuvant, wherein the antigenic component comprises an ESAT6-Ag85B hybrid or a fragment thereof, an immunogenic composition comprising an

adjuvant and a tuberculosis antigen, wherein said adjuvant comprises a solution prepared from an evaporated mixture of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanum and a solvent, wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof ; an adjuvant consisting essentially of a resuspension of an evaporated mixture of a solvent, a surfactant selected from the group consisting of DDA, DODA, or DC Chol and an apolar fraction of a total lipid extract of BCG, M. microti, M. tuberculosis, M. vaccae, M. bovis or M. africanum and a solvent; comprising a tuberculosis antigen, wherein said tuberculosis antigen comprises ESAT6-Ag85B hybrid or a fragment thereof, wherein surfactant is DDA.

Dascher et al teach immunization with a mycobacterial lipid vaccine comprising *Mycobacterium tuberculosis* lipids and DDA (see abstract and pg. 917 column 1 last paragraph). Dascher et al teach a vaccine against tuberculosis with DDA whereby the solution prepared was evaporated (see abstract and pg. 916 column 2 last paragraph) and used cholesterol as carrier lipids.

Anderson et al teach 20020176867 a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis. Anderson et al teach a vaccine, wherein immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis (see abstract, claims, 0027, 0079, whole document in its entirety).

It would have been prima facie obvious at the time the invention was made to modify the adjuvant (disclosed by Lui et al) and to incorporate DDA (disclosed by Dascher et al) because the immune responses induced by the adjuvant DDA is efficient for a TB subunit vaccine (see Lindabald et al see abstract).

One would have a reasonable expectation of success because an adjuvant comprising a cationic surfactant an apolar fraction (as disclosed by Lui et al) is well known in the art.

It would have been prima facie obvious at the time the invention was made modify the composition to incorporate a tuberculosis vaccine of immunodominant antigens ESAT-6 and Ag85B from Mycobacterium tuberculosis (as disclosed by Andersen et al 20020176867) into a composition in order to take advantage clearing or controlling an infection with virulent bacteria.

Furthermore given that Anderson et al (2002/0176867) teach a tuberculosis vaccine comprising the immunodominant antigens ESAT-6 and Ag85B from *Mycobacterium*

tuberculosis. The skilled artisan would have been motivated to use of said antigens in the compositions of Dascher et al. and Lui et al. in order to take advantage clearing or controlling an infection of the virulent bacteria (as disclosed by Anderson et al.) Moreover, since the use of immunodominant antigens ESAT-6 and Ag85B a vaccine composition is known in the art leading to predictable results, their use remains obvious even without an express statement of motivation. See the recent Board Decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007 (citing KSR, 82 USPQ2d at 1396) available at (**http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

Conclusion

5. No claims are allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645